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Systematic review of imaging studies in the lateral orbitofrontal circuit in bipolar type I disorder

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Abstract

Objectives

The aim of this study was to review the available published structural magnetic resonance imaging (MRI) data in bipolar type I disorder, looking for any evidence of a change in size of the structures in lateral orbitofrontal circuits relative to the conceptually unaffected motor circuit. Structures in the motor circuit will thus act as an internal control. We will additionally look at healthy controls as an external control.

Methods

We looked at available literature for studies of lateral orbitofrontal cortex thickness, substructures of caudate, pallidum and thalamus in the lateral orbitofrontal circuit compared with motor cortex thickness and comparable motor nuclei in basal ganglia in bipolar type I. We also looked at bipolar I versus healthy controls.

Results

We found nine studies of subcortical structures, with conflicting results and insufficient resolution for analysis of substructures. Findings in the five studies of cortical structures of interest were more consistent; the lateral orbitofrontal cortex was generally significantly thinner in bipolar I patients whereas, motor cortex was unaffected.

Conclusion

Available data suggests an association between cortical thinning in the lateral orbitofrontal cortex and bipolar disorder type I. The evidence for subcortical structures was inadequate.

Keywords

Bipolar Disorder, Magnetic Resonance Imaging, Frontal Lobe, Basal Ganglia

Background

There appears to be a generalizable functional circuit describing how multiple (but functionally connected) cortical inputs are progressively integrated through specific areas of striatum, pallidum and substantia nigra then through a specific region of thalamus and back to a single area of cortex. The areas involved are circuit-specific. (1) These circuits in humans have been (incompletely) validated in humans by diffusion tensor imaging (DTI) studies. (2)

There is increasing recognition of measurable structural and functional changes in brains of individuals with bipolar disorder. The cardinal feature of bipolar disorder is a manic episode. This and the other primary pathological mood state of depression (3) have been described using a model of a functional circuit. (4)

The lateral orbitofrontal circuit mediates social restraint. Lesions of structures in the lateral orbitofrontal circuit are associated with irritability, tactlessness, fatuous euphoria, impulsivity, overfamiliarity and overt mania, corroborating this hypothesis. Conversely, medial orbitofrontal cortical lesions have been associated with lack of energy, anhedonia, changes in eating and sleeping patterns and depression. (5)

The lateral orbitofrontal circuit starts with cortical input from the lateral orbitofrontal cortex (OFC) (Brodmann areas (BA) 10, 11 and 47), visual and auditory association areas and anterior cingulate area. These project to the ventromedial sector of the caudate nucleus, medial dorso-medial internal globus pallidus and rostromedial substantia nigra pars reticulata. In the thalamus, these project to ventral anterior thalamus and medial dorsal thalamus before closing the loop to the lateral orbitofrontal cortex.

The motor circuit receives inputs from the somatosensory, motor, premotor and supplementary motor areas. The primary striatal structure involved in this circuit is the putamen. Different areas within the putamen are involved with specific body areas. Therefore, both the motor and somatosensory inputs involving the leg will project to the dorsolateral sector of the putamen, while those representing the face will project to the ventromedial sector. The topographically integrated information then projects to the ventro-lateral two thirds of both external and internal globus pallidus and to caudolateral areas of the substantia nigra pars reticulata. This then projects to the ventrolateral thalamus and finally the supplementary motor area. (1)

Recent meta-analyses of fMRI studies have shown (amongst other findings) decreased activity in the orbitofrontal cortex and hyperactivity in the basal ganglia (with mixed results for the putamen) supporting the importance of these circuits in bipolar disorder. It is hypothesised that a relatively underactive lateral orbitofrontal cortex results in disinhibition of the subcortical basal ganglia structures with corresponding increase in activity in limbic structures such as amygdala and hippocampus (which are functionally connected to, but not intrinsically part of the cortico-striato-thalamic tracts.) (4, 6)

Historically, the understanding of the aetiology of bipolar mood disorder has followed the same trends as the other psychiatric disorders. Through much of the latter 20th century, the prevailing view was that it was a functional illness (7) – that is that the pathology was primarily biochemical in nature, and that there were little if any accompanying structural changes. With improving imaging techniques, focus shifted to finding whether there were structural changes accompanying bipolar mood disorder.

Much of the data have been inconclusive, but a 2008 systematic review looked at all of the structural imaging research in bipolar disorder and major depression to identify trends. (Table 1) (8)

Additionally there was a mega-analysis of structural MRI data in bipolar type I disorder published in 2011. Raw data were collected from 11 international research groups (with 321 patients and 442 healthy controls) giving greater statistical power to detect significant volumetric changes. Despite this, the only statistically significant size difference they found was a larger left temporal lobe, a larger right putamen and a larger right ventricle. (9)

The majority of the studies have used either region-of-interest (ROI) analysis or voxel-based morphometry (VBM) Both of these methods have a disadvantage of not being able to account adequately for the folds of the brain and the thickness of the cortex. This may be one of the possible reasons for lack of consistent evidence. Newer methods of software-based automatic are able to analyse cortical thickness, which can show more subtle changes than volumetric measurement. (10)

From the above understanding of mania being expressed as a functional circuit, and with the functional imaging literature confirming deficits in this system, we feel that the available structural literature does not

adequately address the issue of whether there are underlying (or resultant) structural changes accompanying these functional abnormalities. Our hypothesis is that these functional changes will result in a relative thinning of the lateral orbitofrontal and anterior cingulate cortices, with a relative enlargement in the associated basal ganglia and thalamic nuclei in bipolar disorder type I.

Our aim was to review the available published structural magnetic resonance imaging (MRI) data in bipolar type I disorder, looking for any evidence of a change in size of the structures in lateral orbitofrontal circuits relative to the conceptually unaffected motor circuit.

Structures in the motor circuit acted as an internal control, with healthy controls serving as an external control.

Methods

Study Selection

We used an automated, online search strategy. The studies that are relevant to the research question are from the last 20 years, when cataloguing on an online database such as Medline has become the norm.

Two searches were conducted on both Pubmed and Web of Science in December 2011. For our first search, we used a search string "cortical thickness bipolar" Our second search used a combination of bipolar disorder, mania, magnetic resonance imaging, subcortical and basal ganglia (with Mesh terms for Pubmed).

To include as wide a range of articles as possible, we looked at reference lists of the primary studies chosen to identify additional papers not found in the original search string. To check the completeness of our search strategy, we compared the list of papers found to a recent systematic review (8) with specific references to the papers referenced in the subsections dealing with the anatomical areas of interest in bipolar mood disorder type I.

We only included studies that performed structural MRI scans on a scanner of at least 0.5 Tesla magnet strength with a maximum cut size of 2mm and that specifically looked at thickness of lateral orbitofrontal, anterior cingulate or motor cortices or volume of thalamus or basal ganglia structures. There had to be at

least 15 patients with a diagnosis of Bipolar Disorder type I (diagnosed on DSM-IV TR , DSM-IV, DSM-III-R or ICD-10 criteria using a recognised diagnostic instrument) with at least 15 comparable healthy controls. The average age of participants plus or minus one standard deviation had to be between 18 and 55 at time of scan. We excluded patients with co-morbid neurological disorders or major previous head trauma.

Results

Our searches on cortical thickness yielded 33 papers in our Medline search and 60 papers in the Web of Science search. We only found twelve papers meeting our inclusion criteria (10, 12-22), with one additional paper included (11) whose mean age minus one standard deviation was 17 (which was less than our cut-off of 18). The first paper we found which met our inclusion criteria was from 1999, with single studies in 2001 and 2002. From 2005 to 2010, there was an average of one paper a year, and there were four suitable studies published in 2011.

Of the thirteen included studies, ten had between 17 and 26 patients with bipolar disorder type I with the other three having 34(12), 58(11) and 87(13) patients with bipolar type I. Two studies included patients with bipolar disorder type II in their demographic analysis, but distinguished between the two groups in their results (13, 14), while one did not distinguish between bipolar I and II in results (10) although they did state no significant difference between the groups. The largest included study had significant differences between groups for age, gender and race. (20)

Analysis methods

Five papers used manual tracing as their primary analysis method (12, 16, 17, 21, 22), three used voxel based morphometry (11, 18, 19) and four used Freesurfer (10, 14, 15, 20) – an automated method of calculating cortical thickness as well as automatically segmenting subcortical structures. One study used cortical pattern matching to analyse cortical thickness (13). Most scanners used a 1.5 T magnet, with two studies using magnets that are more powerful (11, 18). The slice thickness ranged from 1-2mm with a mean thickness of 1.36mm.

All studies will be reported as comparing bipolar patients with healthy controls unless otherwise stated.

Subcortical Structures

Of significance for our review, none of the included studies had an analysis of substructures of any of the subcortical nuclei. Additionally, the differences between the studies are usually far greater than the differences within a study between healthy controls and patients.

Thalamus

Four papers examined the thalamus. One only gave mean volumes for combined right and left thalamus with no significant volume difference. (22) Another study only gave statistical significance for the combined left and right thalamus, but included volumes individually. It found an increased thalamic volume. (21) The largest of the studies found decreased volume in the left thalamus only. (20) The last study showed no significant differences between bipolar disorder and healthy controls. (16)

Striatum

Only one study looked at combined striatal structures. They only did statistical significance on combined right/left structures, although they did give volumes for left and right structures separately. They found an increased volume, with a medium effect size. (21)

Putamen

Five studies examined the putamen specifically. The same study that only looked at combined right/left thalamus, also only looked at combined putamen volume with an increased putamen size in first episode bipolar disorder patients compared with controls ($p < 0.01$) and a trend to increased putamen size in multiple episode bipolar patients compared with controls ($p = 0.03$). (22)

Hwang and colleagues sub-analysed bipolar patients on treatment and treatment naïve bipolar patients versus healthy controls separately. There were no significant differences between any of these groups. They also examined shape differences in the putamen. There were significant decreases in the drug-naïve group compared with controls in the right putamen's anterodorsal (6.3%) and posteroventral (11.7%) surfaces and the left putamen's ventrolateral (7.3%) and dorsomedial (3.8%) surfaces. There were increases

in the right putamen's anteromedial (3.4%) and posterolateral (4.0%) surfaces. In the drug-treated group, the right putamen showed no shape differences. In the left putamen, there were significant differences in the lateral (2-3% decreases) and medial (up to 10% decrease) surfaces. (17)

The other studies found no significant difference. (13, 16, 20)

Caudate

Most studies found no difference in caudate volume between patients and controls. (12, 16, 17, 20, 22) The study that included adolescents found decreased bilateral caudate volume with a relatively enlarged right caudate on follow-up scan after one year. (11) One study found decreased left caudate volume (but no difference in right caudate) (18) while another found decreased volume in right caudate, with no difference in left. (19)

Hwang examined shape differences in caudate. In drug-naïve patients, there were areas of difference in the posterodorsal (11.2% decrease) and anteroventral (9.4% decrease) in the right caudate with an increase in the dorsal surface. (8.3%) In the left caudate, there was an increase in the anterodorsal surface (4.8%) and there were decreases in anterodorsal (6.3%) and posteroventral (11.7%) surfaces. For the drug-treated group, there were no differences observed in the right caudate. In the left caudate, there was an increase in anteroventral surface (5.6%) and decrease in posteroventral surface (8.8%) in the bipolar patients relative to controls. (17)

Pallidum

Three studies examined the globus pallidus. Strakowski et al. did statistical analysis of combined right/left pallidum, and found increased volume in bipolar patients compared with controls. (22) The other two papers found no statistically significant differences. (12, 20)

Cortical thickness

Studies looking at cortical thickness were more heterogenous in their reporting. Studies generally did not use the same anatomical references, making comparisons difficult.

Lateral orbitofrontal cortex

Three studies examined structures that form part of the lateral OFC. However, the definition of lateral OFC does not exactly match Brodmann's areas. Nonetheless, it comprises the medial inferior frontal gyrus (ventral parts of BA 10 and 47) and the lateral orbital gyrus (lateral part of Brodmann's area 11).

One found decreased thickness in the left lateral OFC, but no difference in the right hemisphere; (20) whereas another found thinner cortex in the right lateral OFC, but no difference on the left. (10) The third found widespread thinning in the left lateral OFC, but also found thinning in parts of the right lateral OFC. (13) (Tables 2, 3)

Anterior cingulate cortex (ACC)

Two studies reported statistically significant decreases in anterior cingulate cortex: one study in both right and left subgenual (BA 32) and dorsal ACC thickness (BA 24); (13) and the other in the left subgenual and dorsal ACC. (20)

Fornito et al. published two papers focussing exclusively on anterior cingulate cortex. The later paper focused exclusively on first psychotic episode bipolar disorder patients, limiting its applicability to a more general group. They found no statistically significant differences, except on post-hoc analysis in the second study where they found male bipolar patients had increased thickness in right subgenual ACC compared with male controls. (15)

The earlier paper notes a significantly decreased paracingulate cortex thickness in the left hemisphere (not mentioned previously, as this area was not part of our review). There is a corresponding trend in the left anterior cingulate cortex to an increased thickness. (14)

A fourth paper found no significant difference (10)

Motor cortex

No studies specifically mentioned the motor cortex, but three studies included graphical representation of the whole brain with colour coding of areas with differences in thickness. There were no thickness changes reported in the precentral gyrus (motor cortex) (10, 13, 20)

Table 4 summarises the main findings.

Discussion

Our aim was to investigate changes in the lateral orbitofrontal circuit in bipolar disorder type I. We hypothesised that there would be cortical thinning in the lateral orbitofrontal and anterior cingulate cortex and no change in the motor cortex, as well as increased volume of related subcortical structures in the lateral orbitofrontal circuit and no changes in the motor circuit structures.

The largest of the included studies (Rimol, 2010) compared 173 schizophrenia patients with 139 bipolar spectrum disorder patients with 207 healthy controls. They noted a statistically significant difference between the ages, gender and race of the different groups, although they did not clarify whether it was specifically significant between bipolar and healthy controls. This could negatively influence the reliability of their results. (20) Further, there were differences between the studies in terms of their illness characteristics. As mentioned, Lyoo et al. did not separate bipolar disorder type II out of the analysis. (10) Nine studies included drug-naïve patients, with one specifically analysing a drug-naïve group, (17) while two studies specifically investigated multiple episode bipolar disorder, (19, 22)(Strakowski, 2002; Molina 2011) illustrating the heterogeneity of the study groups.

Subcortical structures

In the papers that looked at subcortical structures, there were few consistent findings in terms of overall volume and none of the papers specifically mentions sub-structures of subcortical nuclei. The five earlier studies used manual tracing with the later four papers using automated methods.

If we look at the studies overall, the most helpful comparison is in the striatal structures. The caudate (part of which forms part of the lateral orbitofrontal circuit) and putamen (which forms part of the motor circuit) were generally analysed separately. The overall evidence tends to point to a decreased or unchanged caudate volume and an unchanged putamen volume.

However, if one looks at the manually traced, earlier studies as a group compared with the later, automated studies another trend appears. Strakowski and colleagues performed two of the earliest studies and found increased or unchanged volumes in subcortical structures (21, 22) while later studies found no

differences. (12, 16, 17) Additionally, the Strakowski et al. papers are unique in this review in that those two studies are the only ones to perform statistical analysis on combined right and left structures.

Conversely, the later, automated studies all find either smaller or unchanged volumes in subcortical structures – but they do not separately analyse the putamen. As these studies were analysing whole brain, it seems likely that the putamen volume was unchanged and that they did not report it as a negative finding.

Without further sub-analysis of substructures, the thalamic and pallidal studies were unhelpful for our purposes, although Strakowski et al.(21) found an enlarged thalamus while Rimol et al.(20) found a reduced left thalamus.

Manual tracing is still the gold standard for volumetric analysis of MRI studies, so it is tempting to put more weight on those studies. However, even within that subset of studies, only one group of researchers found increased volume (21, 22). Moreover, in two of these (19, 21) is not clear whether there was correction for intracranial volume – which can be a significant confounder. The authors of the later studies were investigating changes throughout the brain, making automated methods more appropriate. They all specifically mention the technical advances used to maximise the accuracy of their automated technique.

On balance of the above, it seems likely that the caudate is relatively smaller than putamen in bipolar disorder. This is contrary to our hypothesis, which proposed an increased size in the subcortical structures in the lateral orbitofrontal circuit. We based this hypothesis on the functional literature that showed increased activity in these structures in bipolar disorder. It may be that over-activity causes excitatory cell-death (and decreased volume) as opposed to synaptogenesis with increased volume. Further research will benefit from more sophisticated methods of small brain structure analysis such as spherical harmonic techniques (17), and controlling for psychosis and exposure to neuroleptic medication (23).

Cortical Thickness

All of the papers found showed at least some areas of thinner cortex in the lateral orbitofrontal and anterior cingulate cortex. It is worth noting that the four studies that used Freesurfer software had variable

areas of thinning or no difference, whereas the one group used an alternate method of cortical pattern matching, using different (not specifically named) software found significantly thinner cortex in all areas of lateral orbitofrontal and anterior cingulate cortex. (13) It is not clear whether the analysis method contributed to this apparent discrepancy – whether by being more sensitive or less specific.

We found no studies that specifically mentioned the motor cortex, but three of the papers reviewed did show clear graphical representation showing no changes in motor cortex thickness, which is in keeping with our hypothesis.

The group that studied only anterior cingulate cortex mention in their discussions a confounder being a normal anatomical variant that is not adequately controlled for in many studies – the absence or presence of a paracingulate sulcus. They note that their controls were not well matched to patients in terms of this variant in the left hemisphere. This may have led to a relative under-estimation of the paracingulate cortex as it would tend to include more cortex from the gyral crown into the paracingulate cortex. As the gyral crown thickness is generally greater than fundal thickness, it may have partially contributed to their finding. Not mentioned by them, but this could also explain a trend to increased thickness of left anterior cingulate cortex in this study. That is, including relatively more of the thinner fundal cortex may have biased the control group's left anterior cortex thickness downwards. They also note in their discussion that they separately analysed cortical volume and surface area – and found no difference in any areas. This reinforces our decision to look at cortical thickness as supposed to the more widely studied cortical volume.

Lyoo et al. found a significant thinning in the left anterior cingulate cortex, (10) while Foland-Ross et al. found significant, widespread, thinning in bilateral anterior cingulate cortex. (13) Neither of these papers mentioned the paracingulate sulcus.

All of the studies that looked at lateral orbitofrontal cortex (OFC) found at least some area of decreased thickness – although they all found it in different regions. Rimol et al. found decreased thickness throughout left lateral OFC with no statistically significant changes in right lateral OFC, (20) while Lyoo et al. found an area of decreased thickness in right lateral OFC with no differences in the left side. (10) Foland-Ross et al. found widespread involvement in the left, but also found an area in the right that had decreased

thickness. (13) What is most striking about these findings is the marked lateralisation in two of the three studies – but with diametrically opposite results in this respect. It is not clear what the reasons for this could be. Both studies had about 90% right-handedness in the patient and control groups. It is possible that a technical error (e.g. mislabelling of the hemispheres) could account for this. It may also be a product of statistical chance. Having said this, there is consistent thinning in the lateral orbitofrontal cortex as a whole.

Limitations

This review was limited by the number and nature of the studies used. Only one article had results we could use across the whole scope of our review (20) and it was limited in that it was primarily a comparison of schizophrenia versus bipolar spectrum (and powered as such.) There were a number of different analytical methods used, which also made interpreting findings difficult. A number of studies showed trends to a finding, but were unable to show significant differences. It may be that they were underpowered for these small differences.

The biggest limitation to achieving the aim of this study was lack of research into sub-structures of basal ganglia nuclei – especially pallidum and thalamus – which was the key to understanding the structures within the circuit. There are inherent technical difficulties in achieving this. It is difficult to delineate sub-structures of such small size accurately and there are no standardised definitions for these in imaging studies.

Conclusion

There is consistent evidence to support our hypothesis of thinning in the cortical structures of the lateral orbitofrontal circuit in bipolar disorder. Contrary to our initial hypothesis, the evidence seems to suggest that there may be a relative decrease in the areas of the striatum involved in the lateral orbitofrontal circuit compared with the putamen (involved with the motor circuit) This evidence is insufficient to consider for diagnostic purposes, but it does help with our understanding of bipolar disorder.

This review is limited by the shortcomings of current structural MRI literature in bipolar disorder. These include different approaches to identifying and describing anatomical structures. It may be that a method

of overcoming the issue of identifying structures and substructures would be to combine a diffusion tensor imaging study with a structural imaging study – using the white matter tracts as a guide to the different substructures within the thalamus, pallidum and caudate nucleus. The number of different image analysis methods and a lack of a standard reporting format pose an additional problem in drawing clear conclusions from the existing literature. Solutions include provision of detailed online reports and making raw data available for pooled studies – which could utilise increasingly powerful analytical tools.

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Table 1

Summary of systematic review of neuroimaging findings in Konarski et al (2008)

Level A	Highly consistent results	Enlarged ventricles Unchanged whole brain volume
Level B	Consistent results	Enlarged striatum Reduced frontal lobe volume Reduced subgenual prefrontal cortex volume
Level C	Discrepant results	Enlarged amygdala
Level D	Insufficient results	Reduced anterior cingulate volume Reduced orbitofrontal cortex volume Reduced dorsolateral prefrontal cortex volume Reduced cerebellar volume
Level E	Inconsistent results	Temporal lobes Thalamus

Table 2

Comparison of right lateral orbitofrontal cortical thickness in bipolar patients and controls

Author		Region	Bipolar vs. Controls
Rimol (20)		Inferior frontal gyrus	NS
		Medial frontal gyrus	NS
Lyoo (10)	Bipolar spectrum vs. controls	Medial frontal cortex (Brodmann Area 10)	D*
	Bipolar I vs. Bipolar II	Medial frontal cortex (Brodmann Area 10)	NS
Foland-Ross (13)		Brodmann Area 11	D†
		Brodmann Area 10	NS

D: Thinner in bipolar disorder compared with controls

NS: No significant difference in thickness

* $p < 0.001$

† $p = 0.006$

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Table 3

Comparison of left lateral orbitofrontal cortical thickness in bipolar patients and controls

Author		Region	Bipolar vs. controls
Rimol (20)		Inferior frontal gyrus	D*
		Medial frontal gyrus	D†
Lyoo (10)	Bipolar spectrum vs. controls	Medial frontal cortex (Brodmann Area 10)	NS
	Bipolar I vs. Bipolar II	Medial frontal cortex (Brodmann Area 10)	NS
Foland-Ross (13)		Brodmann Area 11	D‡
		Brodmann Area 10	D§

D: Thinner in bipolar disorder compared with controls

NS: No significant difference in thickness

* Effect size 0.41

† Effect size 0.40

‡ $p=0.006$

§ $p=0.021$

Table 4

Summary of findings of brain structural volume (subcortical) and thickness (cortical) changes in bipolar disorder

Author	Year	Thalamus		Striatum		Putamen		Caudate		Pallidum		Lat OFC		Subgenual ACC		Dorsal ACC		Motor	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
Strakowski (21)	1999	↑*		↑*															
Brambilla (12)	2001					↔	↔	↔	↔	↔	↔								
Strakowski (22)	2002	↔*				↔*		↔*		↑*									
Hazdenar (16)	2005	↔	↔			↔	↔	↔	↔										
Hwang (17)	2006					↔	↔	↔	↔										
Lyoo (10)	2006											↔	↓	↓	↔	↓	↔	↔	↔
Fornito (14)	2008													↔	↔	↔	↔		
Fornito (15)	2009													↔	↔	↔	↔		
Rimol (20)	2010	↓	↔					↔	↔	↔	↔	↓	↔					↔	↔
Li (18)	2011							↓	↔										
Lisy (11)	2011							↓	↓										
Molina (19)	2011							↔	↓										
Foland-Ross (13)	2011											↓	↓	↓	↓	↓	↓	↔	↔

↔ no statistically significant difference noted

↑ increased in bipolar disorder versus controls

↓ decreased in bipolar disorder versus controls

* Combined right and left structures

University of Cape Town

Appendix A – Protocol

As submitted to, and approved by the Chair of the Dissertations/Doctoral & Masters Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med June 2012.

University of Cape Town

Systematic review of imaging studies in the lateral orbitofrontal circuit in bipolar type I disorder

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Protocol submitted for the purposes of the M Med (Psych) degree of the University of Cape Town

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Background

Rationale

Bipolar mood disorder is a not uncommon (lifetime prevalence for bipolar type I disorder is 0.6%, (Merikangas, 2011) often debilitating psychiatric condition (the World Health Organisation ranks it as one of the leading causes of disability in the world population) (World Health Organisation, 2004) whose aetiology and pathophysiology is relatively poorly understood. The characteristic features of bipolar disorder are periods in a patient's life where they experience one of two primary pathological mood states – mania and depression.

With increasing recognition of bipolar disorder as an important clinical entity, and with a broader scope of relatively effective treatments, there has been a recent trend to think of bipolar type I as the extreme end of a spectrum of bipolar disorders. If one includes a somewhat broader definition of bipolar to include bipolar type II and bipolar disorder NOS the lifetime prevalence increases to 2.4% –which adds an additional 300% to the bipolar type I prevalence. This concept has been debated extensively. Clinically, there is a concern about over-diagnosis of bipolar disorder and over-prescription of relatively toxic mood stabilising agents to disorders where there is less solid evidence for efficacy. For research purposes, the key question is whether they represent the same disease process. If they do not, including a broader spectrum of disorder in bipolar studies may make interpreting results more difficult. (Paris, 2009)

A manic episode is the cardinal feature of bipolar disorder type I. It is a period of intense euphoria (or irritability). Along with this mood, there will be additional symptoms: inflated self-esteem; decreased need for sleep; distractibility; increased goal-directed energy; increase in risky (but potentially pleasurable) activities; flight of ideas; and increased rate of speech.

The other primary pathological mood state is depression. A depressed mood is a period of low mood or anhedonia with additional symptoms including a change in sleep, change in appetite, psychomotor changes, fatigue, diminished self-worth, excessive guilt, poor concentration and thoughts of death. (American Psychiatric Association, 2000)

There appears to be a generalizable functional circuit describing how multiple (but functionally connected) cortical inputs are progressively integrated through specific areas of striatum, pallidum and substantia nigra then through a specific region of thalamus and back to a single area of cortex. The areas involved are circuit-specific. (Alexander, 1986) These circuits in humans have been (incompletely) validated in humans by diffusion tensor imaging (DTI) studies (Lehéricy, 2004) and the primary bipolar symptom clusters of mania and depression have been described in terms of these circuits. (Drevets, 2008)

The lateral orbitofrontal circuit mediates social restraint. Lesions of structures in the lateral orbitofrontal circuit are associated with irritability, tactlessness, fatuous euphoria, impulsivity, overfamiliarity and overt mania, corroborating this hypothesis. Conversely, medial orbitofrontal cortical lesions have been associated with lack of energy, anhedonia, changes in eating and sleeping patterns and depression. (Salloway, 2001)

The lateral orbitofrontal circuit starts with cortical input from the lateral orbitofrontal cortex (OFC) (Brodmann's areas 10, 11 and 47), visual and auditory association areas and anterior cingulate area. These project to the ventromedial sector of the caudate nucleus, medial dorso-medial internal globus pallidus and rostromedial substantia nigra pars reticulata. In the thalamus, these project to ventral anterior thalamus and medial dorsal thalamus before returning to the lateral orbitofrontal cortex.

The motor circuit receives inputs from the somatosensory, motor, premotor and supplementary motor areas. The primary striatal structure involved in this circuit is the putamen. Different areas within the putamen are involved with specific body areas. Therefore, both the motor and somatosensory inputs involving the leg will project to the dorsolateral sector of the putamen, while those representing the face will project to the ventromedial sector. The topographically integrated information then projects to the ventro-lateral two thirds of both external and internal globus pallidus and to caudolateral areas of the substantia nigra pars reticulata. This then projects to the ventrolateral thalamus and finally the supplementary motor area. (Alexander, 1986)

Recent meta-analyses of fMRI studies have shown (amongst other findings) decreased activity in the orbitofrontal cortex and hyperactivity in the basal ganglia (with mixed results for the putamen) supporting the importance of these circuits in bipolar disorder. It is hypothesised that a relatively underactive lateral orbitofrontal cortex results in disinhibition of the subcortical basal ganglia structures with corresponding increase in activity in limbic structures such as amygdala and hippocampus (which are functionally connected to, but not intrinsically part of the cortico-striato-thalamic tracts) (Drevets, 2008; Chen, 2011)

Historically, the understanding of the aetiology of bipolar mood disorder has followed the same trends as the other psychiatric disorders. Through much of the latter 20th century, the prevailing view was that it was a functional illness (McBroom, 1967) – that is that the pathology was primarily biochemical in nature, and that there were little if any accompanying structural changes. With improving imaging techniques, focus shifted to finding whether there were structural changes accompanying bipolar mood disorder.

A landmark study published in *Nature* in 1997 found a significant decrease in grey matter volume in the left subgenual prefrontal cortex in patients with unipolar and bipolar depression compared with controls. (Drevets, 1997) Since then, there have been a number of studies attempting to duplicate, refine and identify new areas of structural changes in mood (and other psychiatric) disorders. Much of the data have been inconclusive, but a 2008 systematic review looked at all of the structural imaging research in bipolar disorder and major depression to identify trends. (Table 1, Konarski, 2008)

Level A	Highly consistent results	Enlarged ventricles Unchanged whole brain volume
Level B	Consistent results	Enlarged striatum Reduced frontal lobe volume Reduced subgenual prefrontal cortex volume
Level C	Discrepant results	Enlarged amygdala
Level D	Insufficient results	Reduced anterior cingulate volume Reduced orbitofrontal cortex volume Reduced dorsolateral prefrontal cortex volume Reduced cerebellar volume
Level E	Inconsistent results	Temporal lobes Thalamus

TABLE 1 – ADAPTED FROM KONARSKI, ET AL. NEUROIMAGING RESULTS IN MOOD DISORDERS (2008)

Early in 2011, there was a “mega-analysis” of structural MRI data in bipolar type I disorder. Raw data were collected from 11 international research groups (with 321 patients and 442 healthy controls) giving greater statistical power to detect significant volumetric changes. Despite this, the only statistically significant size difference they found was a larger left temporal lobe, a larger right putamen and a larger right ventricle. Importantly they found that lithium use had a significant trophic effect on certain brain regions. These lithium treated subjects had larger amygdala (both left and right) and hippocampi (both left and right) as well as an enlarged overall cerebral volume compared to bipolar patients not on lithium. (Hallahan, 2011)

The majority of the studies have used either region-of-interest (ROI) analysis or voxel-based morphometry (VBM.) Both of these methods have a disadvantage of not being able to account adequately for the folds of the brain and the thickness of the cortex. This may be one of the possible reasons for lack of consistent evidence. Newer methods of software-based automatic are able to analyse cortical thickness, which can show more subtle changes than volumetric measurement. (Lyoo, 2006)

From the above understanding of mania being expressed as a functional circuit, and with the functional imaging literature confirming deficits in this system, we feel that the available structural literature does not adequately address the issue of whether there are underlying (or resultant) structural changes accompanying these functional abnormalities. Our hypothesis is that these functional changes will result in a relative thinning of the lateral orbitofrontal and anterior cingulate cortices, with a relative enlargement in the associated basal ganglia and thalamic nuclei in bipolar disorder type I.

Aims and Objectives

The aim of this study is to review the available published structural magnetic resonance imaging (MRI) data in bipolar type I disorder, looking for any evidence of a change in size of the structures in lateral orbitofrontal circuits relative to the conceptually unaffected motor circuit.

Structures in the motor circuit will thus act as an internal control. We will additionally look at healthy controls as an external control.

Objectives

1. To determine whether the reduction in cortical thickness is greater in lateral orbitofrontal cortex and anterior cingulate cortex than in motor cortex in bipolar disorder type I subjects on structural magnetic resonance imaging data.
2. To determine whether the basal ganglia structures in the lateral orbitofrontal circuit (ventromedial sector of the caudate nucleus and medial dorso-medial internal globus) are relatively larger than the corresponding motor circuit structures (putamen, the ventro-lateral two thirds of both external and internal globus pallidus) in subjects with bipolar mood disorder type I on structural magnetic resonance imaging data.
3. To determine whether the areas of the thalamus involved in lateral orbitofrontal circuit (ventral anterior thalamus and medial dorsal thalamus) are relatively larger than the motor circuit structure (ventrolateral thalamus) in bipolar disorder type I on structural magnetic resonance imaging data.
4. To determine whether there is a reduction in cortical thickness in lateral orbitofrontal cortex and anterior cingulate cortex in bipolar disorder type I subjects when compared with healthy controls on structural magnetic resonance imaging data.
5. To determine whether the basal ganglia structures in the lateral orbitofrontal circuit (ventromedial sector of the caudate nucleus and medial dorso-medial internal globus) are larger in subjects with bipolar mood disorder type I when compared to healthy controls on structural magnetic resonance imaging data.
6. To determine whether the areas of the thalamus involved in lateral orbitofrontal circuit (ventral anterior thalamus and medial dorsal thalamus) are relatively larger than the motor circuit structure (ventrolateral thalamus) in bipolar disorder type I when compared with healthy controls on structural magnetic resonance imaging data.

Methods

We will use an automated, online search strategy. The studies that are relevant to the research question are from the last 20 years, when cataloguing on an online database such as Medline has become the norm.

Two Pubmed searches of the Medline database will be done with the search strings: (Cortical thickness bipolar); and ("Bipolar Disorder"[Mesh] AND "Magnetic Resonance Imaging"[Mesh] AND "Basal Ganglia"[Mesh]). Additionally, Web of Science searches will be done with the search strings: (Cortical thickness bipolar); and [(“bipolar disorder” OR mania) AND (“magnetic resonance imaging” OR mri) AND (subcortical OR “basal ganglia”)].

To include as wide a range of articles as possible, we will look at reference lists of the primary studies chosen to identify additional papers not found in the original search string. To check the completeness of our search strategy, we will compare the list of papers found to a recent systematic review (Kempton MJ, 2008) with specific references to the papers referenced in the subsections dealing with the anatomical areas of interest in bipolar mood disorder type I.

Selection Criteria

Inclusion Criteria

Must specifically investigate structural changes

Must use a magnetic resonance imaging scanner of at least 0.5 Tesla magnet strength

Must have a maximum cut size of 2mm

Patients included must be diagnosed with Bipolar Disorder type I diagnosed using DSM-IV TR , DSM-IV, DSM-III-R or ICD-10 criteria using a recognised diagnostic instrument

Must include specific thickness analysis of orbitofrontal cortex, anterior cingulate cortex, motor cortex and specific volumetric analysis of thalamus or corpus striatum

Must be primary studies, whose data has not already been included in this study

Must have more than fifteen patients (in any current mood state) compared with at least 15 healthy controls

The average age of participants plus or minus one standard deviation must be between 18 and 55 at time of scan

Exclusion Criteria

Studies that include patients with co-morbid major neurological disorders or previous traumatic brain injury.

Abstracts for all the papers found using the search strategy detailed above will be analysed separately by two investigators. Where there is doubt about whether the paper meets the selection criteria, it will be included for the second round of selection. The two lists of selected papers will be compared and where differences arise, these will be discussed and compared to the original selection criteria. An attempt will be made to reach consensus, but if this is not possible, the default position will be to include the paper for further analysis.

A second round of analysis will be similar to the first, except two investigators will read the full articles identified in the first selection. The two sets of articles chosen in this second round will again be compared, and where differences arise, reference will be made to the original selection criteria.

Data Extraction

A will be extracted manually directly into a Microsoft Excel spreadsheet. Due to the expected differences in methodology and anatomical labelling, the spreadsheet column headings may be added as needed. An audit of randomly selected articles will be undertaken by a second reviewer to ensure accuracy of this process. Data will be collected on sequentially smaller sub-regions of the areas being investigated and will be entered either as increased or decreased in volume or thickness (in bipolar subjects relative to healthy

controls.) Due to the variability in the reporting of various studies, and due to the limited number of studies explicitly reporting on specific sub-regions, we will not further investigate demographic or disease-state variables, although they will be noted for completeness sake.

Synthesis

Data will be synthesised manually and descriptively. The variability in study design and brain region definitions will tend to make statistical analysis unreliable. Primary focus will be given to papers that report on comparable areas. Therefore, a paper that reports a significant difference in orbitofrontal cortex thickness but no significant difference in motor cortex thickness has more meaning than a paper that reports solely on our putatively affected structures. In whole-brain analysis, where specific mention is made of all volume differences that are statistically significant, it will be assumed that areas not explicitly mentioned as being statistically different in size, have non-significant volume differences.

Study Limitations

Inherent problems in reviews of this kind are the variability in study design of the primary studies. There is variability in definitions of anatomical areas within the brain. Some study designs morph the participants' brains to fit a standardized brain, while others do not. Due to the highly specific nature of this review, many studies do not divide certain structures (especially basal ganglia structures and thalamus) into subdivisions needed and only report on overall increase or decrease in size. Where there is reporting of sub-regions, it is often incomplete - for example, ventral thalamus and not ventral anterior thalamus.

Reporting

This study is intended for publication, and will also form part of training requirements. Depending on the outcome of the review, it may be used to plan further study as part of a wider bipolar disorder project run at the University of Cape Town. The main author will be Dr NJ Yorke and he will be supervised by Dr N Horn, who will also co-author the final publication.

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Appendix B – Author Guidelines

Bipolar Disorders - An International Journal of Psychiatry and Neurosciences will consider for publication full length research papers, brief reports, invited editorials, commentaries, review articles, case reports, and letters to the editors.

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The paper should be submitted in English. The main manuscript components (title page, abstract, text, acknowledgements, disclosures, references, legends, tables, and figures) should begin on a separate page. The pages of the manuscript - text, reference list, tables and legends to figures, in that order, should be numbered consecutively.

Title page

The title page should contain: 1. a concise informative title; 2. author(s)'s names; 3. name of department(s)/ institution(s) to which the work is attributed for each individual author; 4. name, address, fax number, and e-mail address of the author to whom correspondence about the manuscript, and requests for offprints should be referred; 5. if the title exceeds 40 characters (letters and spaces), a running head of no more than 40 characters; 6. a word count for the whole paper.

Abstract and key words

The abstract should not exceed 250 words and should be arranged in a structured fashion to include **objectives, methods, results, and conclusions**. It should state the purpose of the study, basic procedures (study subject /patients / animals, and methods), main findings (specific data and statistical significance), and principal conclusions. For the News and Vies articles, a short (up to 100 words) non-structured abstract should be provided. Below the abstract, provide 3-10 key words that will assist indexers in cross-indexing your article. Use terms from the Medical Subject Headings list from [Index Medicus](#), whenever possible.

Introduction

Present the background briefly, but do not review the subject extensively. Give only pertinent references. State the specific questions you want to answer.

Patients and methods / Materials and methods

Describe selection of patients or experimental animals, including controls. Do not use patients' names or hospital numbers. Identify methods, apparatus (manufacturer's name and address), and procedures in sufficient detail to allow other workers to reproduce the results. Provide references and brief descriptions of methods that have been published. When using new methods, evaluate their advantages and limitations. Identify drugs and chemicals, including generic name, dosage and route(s) of administration. Authors must indicate that the procedures were approved by the Ethical Committee of Human Experimentation in their country, and are in accordance with the Helsinki Declaration of 1975. All papers reporting experiments using animals must include a statement in the Materials and Methods section giving assurance that all animals received humane care. The authors accept full responsibility for the accuracy of the whole content, including findings, citations, quotation,s and references contained in the manuscript.

Results

Present results in logical sequence in tables and illustrations. In the text, explain, emphasize, or summarize the most important observations. Units of measurement should be expressed in accordance with Système International d'Unite (SI Units).

Discussion

Do not repeat in detail data given in the Results section. Emphasize the new and important aspects of the study. Relate the observations to other relevant studies. On the basis of your findings (and others') discuss possible implications / conclusions. When stating a new hypothesis, clearly label it as such.

Acknowledgements

Acknowledge only persons who have made substantive contributions to the study. Authors are responsible for obtaining permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions. Authors are expected to disclose any commercial or other relationships that could constitute a conflict of interest. All funding sources supporting the work should be acknowledged.

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Tables

Tables should be numbered consecutively with Arabic numerals. Type each table on a separate sheet, with titles making them self-explanatory. Include the year of publication and reference number along with the author(s)' name for any citations listed in the table. Identify all acronyms and superscript letters and symbols in the legend.

Illustrations

All figures should clarify the text and their numbers kept to a minimum. Details must be large enough to retain their clarity after reduction in size. Illustrations should preferably fill single column width (81 mm) after reduction, although 2/3 page width (112 mm) or full page width (168 mm) will be accepted if necessary. Magnifications should be indicated in the

legends rather than inserting scales on prints. Line drawings should be professionally drafted and photographed; halftones should exhibit high contrast.

Where possible, authors should send digital versions of each figure saved as a separate file in TIFF or EPS format.

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Legends should be typed double-spaced in consecutive order on a separate page. They should be brief and specific. If micrographs are used, information about staining methods and magnification should be given.

Abbreviations, symbols, and nomenclature

They should be standardized and in accordance with ELLIS G (ed.). Units, symbols and abbreviations. The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE, 1975.

References

Number references (in parentheses) consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals (in parentheses). All references cited, and only these, must be listed at the end of the paper. References should be according to the style used in Index Medicus and International list of periodical title word abbreviations (ISO 833). All references must be provided in Vancouver style.

Examples:

1. International Steering Committee. [Uniform requirements for manuscripts submitted to biomedical journals](#). N Engl J Med 1997; 336: 309.
2. Gershon S, Soares JC. Current therapeutic profile of lithium. Arch Gen Psychiatry 1997; 54:16-20.
3. Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997; 41: 86-106.
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Psychopathol 2011; doi:10.5127/jep.014311.

If a citation with page numbers is available, these details should be used instead of the doi number.

References in Articles

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